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December 23 , 2004

VIA FACSIMILE, confirmed by 1st class mail

Examiner Sharon Lee Howard
Group Art Unit 1615
United States Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Re: Patent Application Serial No. 10/072,177
Applicants: Fischell et al.
Filing Date: 02-11-2002
Title: "Devices and Methods for Reducing Scar Tissue Formation" ("the subject '177 application")
Group Art Unit 1615

Dear Examiner Howard:

Per our phone conversation on Monday, December 13, 2004, this is to provide our views with respect to several positions taken in the subject '177 application in the name of Robert E. Fischell et al. The subject '177 application corresponds to Patent Application Publication US 2003/0152609 (hereafter "PAP '609").

Background: The subject '177 application was filed on February 11, 2002. In those initial-filing documents no claim of priority to any prior application was made.

In a document styled PETITION TO ACCEPT AN UNINTENTIONALLY DELAYED CLAIM, under 35 U.S.C. §120, for the benefit of a prior filed application mailed on May 2, 2004, (*i.e.*, more than 2 years after its filing date) Fischell *et al.* petitioned to claim the priority of grandparent application 09/705,999 filed November 6, 2000, now abandoned ("the '999 grandparent application"), and parent application serial number 09/772,693 filed January 31, 2001, now issued US patent 6,534,693 (hereafter either or both of "the '693 parent application" and "the '693 patent").

Per a DECISION ON PETITION under 37 CFR §1.78(a)(3) mailed August 18, 2004, the Fischell *et al.* petition mailed on May 2, 2004, was granted. On the second page of that August 18, 2004 letter Lead Petitions Examiner, Francis M. Hicks noted in bold, underlined, italics, as follows:

> ***be construed as meaning that the instant application is entitled to the benefit of the prior-filed applications. In order for the instant application to be entitled to the benefit of the prior-filed applications, all other requirements under 35 U.S.C. § 120 and 37 CFR 1.78(a)(1) and (a)(2) must be met. Similarly, the fact that the corrected Filing Receipt accompanying this decision on petition includes the prior-filed applications should not be construed as meaning that applicant is entitled to the claim for benefit of priority to the prior-filed applications noted thereon. Accordingly, the examiner will, in due course, consider this benefit claim and determine whether the instant application is entitled to the benefit of the earlier filing date.*** (Emphasis in original)

In this portion of our letter, we will show that, in no sense, are the claims of the subject '177 application entitled to the benefit of a claim of priority to either the parent '693 application or the grandparent '999 application. Thus, the examiner is strongly urged to deny the Fischell *et al.* claim of priority. The undersigned submits that Fischell *et al.* pending claims are unpatentable, in view of the prior art and disclosure issues discussed herein. In short, the presently pending claims of the subject '177 application are unpatentable on the basis of new matter and prior art that cannot be overcome by the simple double-patenting rejection already raised and responded to (by filing a terminal disclaimer) in this prosecution.

This '177 Application is Not Entitled to Claim the Benefit of the Parent '693 Application in Accordance with Fischell, et al.'s Own Assertions.

First, it should clearly be remembered that the subject '177 application is a "continuation-in-part" ("CIP") of parent application '693. Thus in accordance with well-known principles there is likely to be, and in fact is, substantial added disclosure which would be considered "new matter" under 35 U.S.C. § 132. Early in the application, at paragraph [0003] Fischell *et al.*, admitted they were not entitled to any legitimate claim of priority from the parent '693 application to the subject '177 application by stating:

> "[0003] U.S. patent application Ser. No. 09/772,693 by R.E. Fischell, et al, filed on Jan. 1, 2001 [sic, January 31] describes various means and methods to reduce scar tissue formation resulting from a surgical procedure. However, this patent application does not describe a cytostatic anti-proliferative surgical wrap that is placed around some human tissue where there is a risk of formation of scar tissue. Although several companies have developed products (such as sheets of biodegradable mesh, gels, foams and barrier membranes of various materials) that can be placed between these structures to reduce the tissue growth, none are entirely effective." (Emphasis supplied)

Claim 1 of the '177 application as filed, and as it remains after filing an amendment on March 25, 2004, reads as follows:

> "Claim 1 (original): A cytostatic anti-proliferative surgical wrap sheet of material adapted for being wrapped generally around tissues of a human body at the site of a surgical procedure, the sheet of material having a cytostatic anti-proliferative drug attached, the action of the cytostatic anti-proliferative drug being a reduction in the generation of scar tissue, the cytostatic anti-proliferative drug being selected from the group that includes sirolimus, anti-sense to c-myc (Resten-NG), tacrolimus (FK506), Everolimus and the any functional analog of sirolimus including: SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin, 7-epi-thiomethyl-rapamycin, 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline." (Emphasis supplied)

Thus, by Fischell *et.al.*'s own admissions in its specification, the parent '693 application does not provide a basis for a claim of priority such as, for example, to that of pending claim 1. Under well-settled precedent, any claim in a CIP application which has language added to the CIP is accorded the filing date of the CIP application. Augustine Medical, Inc. v. Gayman Industries, Inc., 181 F.3d 1291 (Fed.Cir. 1999). Thus, Claim 1 of the '177 application has a priority claim of February 11, 2002 *viz.*, the filing date of the application itself, and is not entitled to the benefit of any earlier-filed application under 35 U.S.C. §120.

The differences in tissue anatomical configuration as well as Application Geometry is Medically Critical.

It is conceivable that the examiner may consider the language "adapted for being wrapped generally around tissues of a human body," of the subject '177 application, Claim 1, not to be significantly different from the "adapted for implantation between tissues of a human body" of the '693 issued patent. That logic would support the double-patenting rejection mailed 12/18/03 if the subject '177 application were entitled to a priority claim from the '693 parent application. Nothing could be further from the medical truth.

Differences between Tissues based on Anatomical Configuration:

The examiner's attention is directed to the following example, which illustrates the difference between the configurations of two different kinds of tissue: a piece of muscle and a segment of a blood vessel. The example will also demonstrate how the difference in anatomical configuration between these two tissues impacts the use of and has downstream treatment implications when a drug-containing material is wrapped around such a tissue segment.

Muscle and blood vessel are both examples of body tissues and wrapping of a material around either tissue is usually accomplished surgically – *i.e.* both are examples of a surgical

implantation. However, there is a distinct difference between a piece of muscle, which is an example of a solid (*i.e.* non-hollow) tissue of the human body, and a hollow, generally tubular tissue or organ, for example a segment of bowel (jejunum, ileum, colon) or segment of blood vessel (*e.g.* artery or vein). These hollow, tubular tissue segments can be involved in the creation of an anastamosis (see page 11 for a detailed discussion on anastamosis). Once, for example, an anastamosis involving blood vessels (a vascular anastamosis) is created, a sequence of events that leads to internal stenosis (as a result of neointimal formation or neointimal hyperplasia) can be initiated as detailed in the section on anastamosis on page 11. Neointimal hyperplasia that leads to narrowing of the blood vessel is unique to the blood vessel and is linked to the tri layered construction of the blood vessel wall, very different from the anatomical configuration of a piece of muscle. In fact, between a piece of muscle and a segment of blood vessel, besides the differences in anatomical construction there are also issues related to the pressure and dynamics of blood flow within these blood vessels that influence the formation of neointimal hyperplasia, internal to the blood vessels. Since this internal event (neointimal hyperplasia causing narrowing of the blood vessel) is irrelevant in tissues like muscle, the downstream (treatment) implications of wrapping a material containing a drug around a blood vessel are profoundly different from wrapping such a material around a piece of muscle.

Application Geometry:

Adapting (converting) the flat sheet of matrix to a wrap configuration (i.e. a cylinder if the matrix is wrapped around a blood vessel) is more than a change in the geometry of the matrix. This seemingly simple geometric change or change in the shape of the matrix has significant treatment implications. A drug containing surgical wrap or sleeve is ideally suited for treating pathologies internal to the blood vessel or anastamosis (*e.g.* vessel stenosis resulting from neointimal hyperplasia). Since the placement of a wrap around a tissue results in the formation of an external cover around that tissue, in the case the wrap in question contains a drug, (the subject of this present patent application discussion) such a drug containing wrap has the potential to treat pathologies internal to the tissue. Stated differently, one would be motivated to specify and describe the use of such a drug eluting wrap only if there was intention to treat internal pathologies such as neointimal hyperplasia.

Hence,

- wrapping a drug containing material around a tissue is a deliberate specialized form of surgical implantation done with a specific intent and purpose, and,
- as illustrated in the above example , the indication and subsequent effect of placing such a drug containing wrap is not the same for all body tissues.

However, it is not surprising that Fischell *et al.* did not describe such a surgical wrap in either the '999 grandparent application or the '693 parent application, since Fischell *et al.*'s focus in the '999 application as well as in the issued '693 patent was the treatment of post operative adhesions (pathology as a consequence of surgery, found external to the blood vessel, muscle or other tissues of the body). In fact, the benefit and value of the wrap for treating such internal

pathologies was not completely recognized and described by the Fischell *et al.* until his much later May 7 and May 30, 2003 applications (see attached chart).

Teaching the treatment of post operative adhesions using a matrix sheet combined with a drug (the focus of the specifications of the Fischell '693 patent and '999 application) does not teach the use of the matrix combined with a drug for the treatment of neointimal hyperplasia or neointimal formation causing stenosis for example at or internal to an anastamotic site or stenosis of the lumen of a graft or blood vessel. This is the focus of the specifications and basis of the issued claim of the Iyer et al US patent 6,726,923 discussed in detail below.

Prior Art Renders Certain of the Claims of the '177 Application Unpatentable Regardless of the Double Patenting Issue.

Because claims 1-4, and 13-18, (in which the "adapted for placement generally around the tissue of a human subject" language is used) of the subject '177 application are only entitled to the actual filing date of February 11, 2002, an extensive array of prior art prevents those claims from being issued.

For example, Iyer *et al*, U.S. 6,726,923 claims a priority of January 16, 2001, and a U.S. non-provisional filing date of January 16, 2002 *viz.*, more than a year earlier than the filing date of the subject '177 application. The limited disclosure of the '177 specification should be contrasted with the detailed disclosure of the Iyer *et al.* specification. Pertinent disclosures found in both the January 16, 2001 provisional application of Iyer *et al.*, and the issued Iyer *et al.* '923 patent are shown below:

Page 3 Line 3:

> "In one embodiment, the present invention is a prosthetic device placed on the outer surface of the vessel or graft which elutes a smooth muscle cell proliferation–inhibiting (antiproliferative) drug such as Taxol® or similarly functioning drugs." (Emphasis supplied)

Page 3 Line 10:

> "Thus in one aspect, the present invention is a method of inhibiting smooth muscle cell proliferation of a vascular access graft or shunt by the gradual elution or timed release of a drug from outside the vascular access site vessel wall to the vessel interior." (Expanded upon at column 5, line 22, and column 5, line 49 of the '923 Iyer *et al.* patent). (Emphasis supplied)

Page 3 Line 19 ('923 patent, Col. 5, Line 64):

> "A third embodiment of the present invention is a method of inhibiting stenosis of hemodialysis access graft comprising the method of placing a prosthetic device(described above) over a graft or vascular structure and/or at the **site of anastamosis**...." (Expanded upon in the paragraph starting at column 7, line 36 of the '923 patent). (Emphasis supplied)

Page 4 Line 12:

> "In one aspect, this invention is a prosthetic device consisting of an inner protein layer combined with a cytotoxic or antiproliferative drug such as Taxol®....Collagen is a particularly preferred example of such a protein...."

Page 6 Line 22:

> "As is noted above, Taxol is a particularly preferred antiproliferative drug for use in the present prosthesis. Taxol is representative of a family of drugs called anti proliferative medications. OTHER REPRESENTATIVE MEMBERS OF THIS FAMILY INCLUDE RAPAMICIN [SIC], ANGIOPEPTIN, VASSENOID, ANTISENSE GENETIC MATERIAL, ETC." (Expanded upon at column 10, line 61 of the '923 patent). (emphasis supplied)

Hence, Iyer *et al.* in their provisional application of January 16, 2001 as well as in the issued Iyer '923 patent disclose placing a prosthetic device, *e.g.*, a biodegradable matrix like a sheet of collagen, combined with an anti proliferative drug like rapamycin at an anastamotic site. Both are prior art to the subject '177 application if it is not given the §120 benefit of priority.

Scar tissue formation "at the site of the surgical procedure"

The examiner's attention is directed to the series of patents of Carol Wright *et al.* While the Wright *et al.* patents are primarily directed to coated stents, there is disclosure in *e.g.*, U.S. 6,273,913, filed on April 16, 1998 and issued on August 14, 2001, starting at column 7, line 1 *et seq.*:

> "4. Experimental Method-Pericardial Delivery
>
> A. Polymeric Sheet Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly (caprolactone-gylcolide) or non-degradable polymer, e.g.,

> polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10μ to 1000μ."

In fact, in prosecution of the '693 parent application Fischell *et al.* had an opportunity to comment upon Carol Wright U.S. 6,273,913 in an Information Disclosure Statement filed on 10/19/2002. Fischell *et al.* distinguished his invention on the basis of the distinction between treating internal and external pathologies as follows:

> "In U.S. Patent Number 6,273,913, Wright *et al* describe a stent with rapamycin (sirolimus) for the prevention of restenosis after stent implantation. Col 6, lines 16-19, of the '913 patent describe the use of rapamycin for prevention of neointimal proliferation and restenosis which are typically problems associated with balloon angioplasty and stent implantation. Col 7, lines 1-8 describes such a wrap of a sheet of material around a target vessel for preventing scar tissue formation **inside that vessel.** The applicants respectfully contend that that the sheets of material of the present invention [i.e., the invention of the '693 parent application] are for placement between tissues of the human body after a surgical procedure (see Fig 5). The purpose of the sheets of material being to reduce scar tissue formation at the site of that surgical procedure. The '913 patent only envisions and only mentions wraps around a vessel for the treatment of that vessel following an intraluminal procedure without any drawing or other description that would allow a person of ordinary skill in the art to make such a device. In contradistinction to the '913 patent, the present invention illustrates and teaches essentially flat sheets with sirolimus or analogs (see Fig 1), a suture (see Figs 2 and 3) and inserted between surgically separated tissues of a human subject (see Fig 5)." (Emphasis supplied)

Using the construction of a vascular anastamosis as an example of a surgical procedure, scar tissue formation at the site of the anastamosis (the site of the surgical procedure), can be internal and/or external to the anastamosis site. In distinguishing from Wright, Fischell points out that Wright's description is for preventing internal scar ("inside that vessel"). If, as indicated by Fischell, scar tissue internal to the site of anastamosis is excluded, what is remaining as a treatment target is scar tissue external to the site of the anastamosis. An example of scar tissue external to the site of anastamosis is post-operative adhesions.

To the extent the examiner is inclined to read the "adapted for" language out of the claim, leaving what would amount to a "surgical wrap, sheet of material" it should be noted that extensive prior art discloses rapamycin attached to sheet materials:

US Patent: 6,231,590
Modified stent useful for delivery of drugs along stent strut
Filed: July 12, 1999
Issued: May 15, 2001
Inventors: Slaikeu et al

In the '590 patent, Slaikeu *et al.* disclose a composition comprising Rapamycin (Col. 7, lines 48-51) attached to a sheet (inner tie coating 204) shown in Fig 2.

US Patent: 5702715
Title: "Reinforced Biological Sealants"
Filed: 10/27/95
Issued: 12/30/97
Inventors: Nikolaychik et al

a. In the '715 patent, Nikolaychik et al discloses the compositions for a fibrin matrix, a reinforced biological sealant. The biological sealant comprises a combination of fibrinogen and thrombin which results in the formation of fibrin – a biodegradable matrix or material.
   i. "The sealant comprises fibrinogen composition and a thrombin composition layered on the fibrinogen composition...."
   ii. "In one preferable form of the present invention, both the fibrinogen and thrombin composition are **films...."**
   iii. "Means are provided for activating formation of fibrin from the fibrinogen and thrombin films so as to form a fibrin **mesh..."**

b. In the '715 patent, Nikolaychik et al discloses a "film of fibrinogen and thrombin" and a "fibrin mesh".
c. "FIG. 1 illustrates alternative shapes of the reinforced biological sealant of the present invention". (emphasis supplied)
   i. FIGS. 1A, B and C illustrate planar films. (emphasis supplied)
   ii. FIG. 1A illustrates a planar thrombin or fibrin film.
   iii. FIGS. 1B and C illustrate layered reinforced films.
   iv. FIG. 1D illustrates interlocking between fibrinogen/thrombin films.
   v. FIG. 1E illustrates a ring structure, suitable for application as an interphase.
   vi. FIGS. 1F through J illustrate the reinforced films of the present invention adapted to contact cylindrical structures, such as blood vessels. (emphasis supplied)
   vii. FIG. 1F is a structure adapted to fit a half-cylindrical with side attachments.
   viii. FIG. 1G is adapted to fit a cylindrical shape with a top flange.

ix. FIG. 1H is adapted to fit a cylindrical shape. (emphasis supplied)
x. FIG. 1J is adapted to fit a cylindrical shape with top flange.

d. In the '715 Nikolaychik et al patent there is also reference to the addition of medications ....for topical (local) delivery.
   i. "In another embodiment, medications, such as antimicrobials or stimulators/inhibitors, are included in the reinforced fibrinogen film to effect topical delivery of the medication to the wound." (emphasis supplied)
   ii. "It is an object of the present invention to provide a reinforced biological sealant useful in providing hermetization and hemostasis to wounds, including surgically open surfaces and sutures." (emphasis supplied)
   iii. "It is another object of the present invention to provide a reinforced biological sealant useful in providing topical delivery of medications to wounds, including surgically open surfaces and sutures."(emphasis supplied)

US Patent: 5,660, 873
Coating intraluminal stents
Filed: September 1994
Issued: August 1997
Inventors: Nikolaychik et al

In the '873 patent Nikolaychik et al disclose fibrin coatings (a biodegradable matrix) and additives to the fibrin coatings. A number of additives including inhibitors of smooth muscle cell growth ("antiproliferatives") and antibiotics are disclosed. Nikolaychik discloses macrolide antibiotics. Rapamycin is one example of a macrolide antibiotic.

In summary, Nikolaychik et al disclose

i. A biodegradable matrix like fibrin,
ii. The matrix can be in the form of a sheet or a mesh
iii. The matrix can be combined with drugs for topical (local) delivery.
iv. The drugs include anti proliferatives and antibiotics including macrolide antibiotics.

Morris *et al.*, U.S. 5,646,160 describes at column 11, line 34, the administration of a compound using "a transdermal patch containing the active compound and a carrier...." One of the compounds prominently discussed by Morris is rapamycin. To one skilled in the art a transdermal patch *e.g.*, a motion sickness patch, is an example of combining rapamycin to a flat matrix.

Hence, combining anti proliferative drugs to a flat sheet of matrix wherein the matrix is in the form of a mesh has been described and is prior art to Fischell.

Claim 5 relates to a drug attached to a surgical suture. It will not be further discussed here.

With respect to instant Claims 6, we respectfully request the Examiner's attention be directed towards the following terms in the claim language, emphasized in bold font:

> **Claim 6**: "A cytostatic anti-proliferative **drug attached to a sheet for placement at an anastamosis of a vessel of the human body,** the drug and sheet combination being adapted **to prevent narrowing of the vessel at the site of the anastamosis of that vessel**"....

There is no disclosure in either the grandparent '999 or the '693 parent applications to support the use of the drug combined to a sheet or mesh by contacting an anastamosis to treat neointimal tissue internal *i.e.*, narrowing of the vessel, at the site of the anastamosis.

An **anastamosis** refers to the "joining together" of two, hollow, generally tubular conduits. Examples of such anastamosis include vascular anastamosis (conduits involve blood vessels), bowel anastamosis (conduits involve loops of bowel *e.g.* colon) etc.

Both conduits involved in the creation of the anastamosis may be tissue or organ segments, or one of the conduits involved in the creation of the anastamosis may be made of a prosthetic material like polytetrafluoroethylene (PTFE). Some examples of conduits involved in the creation of a **vascular anastamosis** are shown in the Table below:

Conduit 1	Conduit 2	This is an example of...
Mammary **Artery**	Coronary **Artery**	Arterial-Arterial Anastamosis
Radial **Artery**	Cephalic **Vein**	Arterial-Vein Anastamosis. This is also referred to as a Fistula and is an anastamosis frequently performed in patients needing Hemodialysis
PTFE	Cephalic Vein	An anastamosis using a prosthetic conduit like PTFE. One end of the PTFE tube is anastamosed to a vein in the arm, the other end is anastamosed to an artery. In other words, the prosthetic PTFE conduit functions as a vascular segment substitute, is interposed between and helps connect the artery and the vein. This arrangement is frequently referred to as an A (arterial)-V (Venous) graft and is another common operation performed in patients needing Hemodialysis.
PTFE	Artery	An anastamosis between a prosthetic conduit like PTFE and an artery. An example of such an operation is when the PTFE prosthetic conduit is used to bypass a narrowed or occluded segment of artery (for example in the leg)

Instant claim 6 refers to a cytostatic antiproliferative drug attached to a sheet for placement at an anastamosis, Claim 13 refers to a surgical procedure, and dependent claims 14 specifies a vascular surgical anastamosis as an example of such a surgical procedure with further specific examples of vascular anastamotic procedures in instant claims 17 and 18.

The surgical region at the site of an anastamosis must be viewed as two anatomically separate areas with their own separate and identifiable patho-physiologies and pathologies.

i. **Areas external to the site of anastamosis**: An example of pathology involving the area external to the site of the anastamosis is post-operative adhesions resulting from the surgical separation of the tissues external to the blood vessels, in cases where the anastamosis involves the vascular system.

ii. **Areas internal to the site of anastamosis**: An example of pathology involving the area internal to the site of anastamosis is the proliferation of neointimal tissue (intimal hyperplasia - a manifestation of the vasculoproliferative response). This neointimal tissue encroaches on the lumen of the vessel resulting in lumen stenosis or lumen narrowing. In the case of hemodialysis A-V grafts, this stenosis or narrowing typically occurs near the venous end of the anastamosis. As the stenosis becomes progressively more severe, the graft becomes dysfunctional and hemodialysis is suboptimal. If the stenosis is not treated, it eventually leads to occlusion and graft failure.

Although the creation of an anastamosis usually involves a surgical procedure, there are certain unique events that occur internal to the creation of these anastamosis, especially when the anastamosis involves vascular conduits *i.e.*, a vascular anastamosis. In other words, these internal events are not seen with every surgical procedure and needs the creation of an anastamosis (especially unique to the vascular system) and or other breach of the vascular wall and are related to the tri-layered anatomical construction of the blood vessel wall. These internal events that lead to the stenosis of the blood vessel are separate and distinct from the postoperative adhesions that are external to the creation of these anastamosis.

It is the post operative adhesions, EXTERNAL to the anastamosis site that Fischell *et al.* set out to treat - using the "rapamycin combined to a sterile sheet or mesh that is designed to be placed within internal body tissues to prevent the formation of post operative adhesions".

The specifications in the 09/705,999 application (alleged to be the grandparent of this subject **10/351,207** application), which was filed on Nov. 6, 2000 (subsequently abandoned), and the continuation-in-part parent application, which was filed on January 31, 2001, serial number 09/772,693 (now U.S. patent 6,534,693, issued March 18, 2003), both relate to the use of a drug combined to a sheet or mesh to prevent formation of postoperative adhesions.

As is noted in the Abstracts of both the '999 and the '693 applications:

> "This invention is an anti-proliferative drug placed onto or within a sterile sheet or mesh that is designed to be placed between internal body tissues to prevent the formation of post-operative adhesions, which adhesions are really scar tissue formation...." (emphasis supplied)

We respectfully request the examiner to recognize the unique nature of the anastamosis that differentiates this site from other surgical sites and to further recognize that the placement of a sheet of material containing an antiproliferative drug has the potential to treat pathologies internal to the site of anastamosis.

We wish to emphasize that in the parent '693 application, and in the grandparent '999 application, Fischell *et al.* have neither described the placement of a sheet of material with an attached drug at the site of anastamosis, nor do they include in the specification the use of the drug to treat such pathologies internal to the anastamosis.

In their response to the first office action by Examiner Kim Lewis (application 10/351,207), Fischell *et al.*(see chart) makes the following statement:

> "This application is a Continuation of co-pending application 09/772,693 filed on 1/31/01 which is a continuation-in-part of application 09/705,999 filed 11/06/00. The '999 application to Fischell et al clearly discloses "a sheet of material" impregnated

with rapamycin and the '693 patent teaches using the sheet of material with an anastamosis." (emphasis supplied)

This is a vast simplification, and fails to accurately characterize the limited disclosure in the '999 application and the '693 application (and '693 patent). In fact:

a) The ONLY reference to "an anastamosis" in the '999 application is in the context of using a suture or a staple with the intention of reducing cellular proliferation where the sutures penetrate through the human tissue. There is no reference or mention of "using a sheet of material with an anastamosis" in the November 2000 application. (emphasis supplied)

b) In the '693 application filed by Fischell on January 31st 2001, (which subsequently matured into U.S. Patent 6,534,693) there is an additional reference to an anastamosis site. However, once again, there is no reference or mention of "using a sheet of material with an anastamosis" in the January 2001 application. The reference to the term "anastamosis" in the January 2001 application is described below

"Still another application of these concepts is for aterio-venous fistulas that are used for kidney dialysis patients. These devices (which are also called a-v shunts) are used to connect an artery in an arm to a large vein in the same arm. The plastic a-v shunt is then penetrated by comparatively large needles, through which the patient's blood is cleansed typically every other day. A frequent cause of failure for these shunts is caused by proliferative cell growth at the anastamosis where the shunt is joined to a vein. By having sutures coated with an anti-proliferative agent and by coating the interior and/or exterior of the a-v shunt with an anti-proliferative agent it is expected that the time for maintaining adequate blood flow through the vein will be extended."

The above paragraph appears for the first time in the Fischell 09/772,693 Jan 31st 2001 application and is not present in their November 2000 application. The disclosure in the above description relates to coating sutures as well as coating the interior and exterior surface of the A-V shunt with an antiproliferative agent. This disclosure does not teach using a sheet of material impregnated with rapamycin, with an anastamosis.

There is no basis for Fischell *et al*'s purported claim of priority to the 693 or 999 applications for claim language that uses the terms " placing a sheet material containing a cytostatic drug at the site of anastamosis," "to prevent narrowing of the vessel at the site of anastamosis," an internal phenomenon. The disclosure in the '999 application and '693 patent and application relates only to postoperative adhesions, an external phenomenon. As is noted above at page 2 Fischell *et al.* intentionally and knowingly admitted that the parent '693 application does not provide disclosure relating to such pathologies. Thus, the prior art noted above is equally applicable to claim 6 and its' dependent claims 7 and 8.

Claims 9-12 relate to a "systemic release into the human subject" of a combination of drugs. It is not believed that either the Fischell *et al.* grandparent '999 application or the parent '693 application provides enablement for such claims. A similar analysis follows with respect to dependent claims 10-12.

Claims 13-18 of the subject '177 application are discussed above.

Claims 19-21 relate to placement of an "ointment onto the skin"...and "placing a bandage over the ointment,...." The ointment includes "a cytostatic anti-proliferative agent" which includes rapamycin. Topical administration of rapamycin is probably very well known.

Claim 22 of the '177 Application is Not Limited by Any "Adapted For" Language as is Extensively Discussed Above.

Claim 22, as Amended, Provides as Follows:

> Claim 22 (currently amended): A sheet for placement at or near the site of a surgical procedure to reduce the formation of scar tissue and adhesions, the sheet including a cytostatic drug that is released from the ~~mesh or~~ sheet over a period that is longer than a day, the cytostatic drug being capable of preventing the initiation of DNA replication of cells in the vicinity of the ~~mesh~~ sheet by acting as a cell cycle mitosis inhibitor that acts on the cells in the vicinity of the ~~mesh~~ sheet at or before the S-phase of cellular mitosis. (Amended as shown per Amendment filed March 29, 2004).

Certainly no claim of priority to any earlier application can be made since the language of Claim 22 first appears in the subject '177 application. It will not be further discussed here.

CompareRite™ Comparison of the '693 Issued Patent and the Subject '177 Application

A CompareRite™ computer-generated language comparison of the '693 Issued Patent versus PAP 2003/0152609 (the patent application publication of the subject '177 application) is attached. Any doubt as to the extensive changes between the parent '693 parent application and the present '177 application is quickly dispelled by review of the attachment. The format is ~~line out~~ indicates deletions and **bold** indicates insertions.

Other pending Fischell *et al.* applications.

It is to be noted that, in derogation of its duty of candor, Fischell *et al.* have neglected to bring to the attention of the examiner in this application all of the other pending Fischell *et al.* applications. Those applications tend to be spread among different examiners in different Group Art Units, and many times with different SPE's. For your information, we are attaching hereto a chart showing the status of the Fischell *et al.* applications as of December 15, 2004. Our

submission of the information relating to the Fischell *et al.* applications should, in no sense, be construed as discharging Fischell *et al*'s obligation of its duty of candor to the Office.

One of the Fischell *et al.* Applications *viz.* 10/351,207 is being handled by Examiner Kim Lewis.

Some of the priority issues discussed above were more extensively analyzed in a letter to Examiner Kim Lewis dated November 24, 2004, and entered into the file history of SN 10/351,207 on November 29, 2004. The examiner is invited to review the electronic prosecution history of 10/351,207 application, particularly the undersigned's letter faxed November 29, 2004, which is available in the electronic file wrapper.

Respectfully submitted,

MICHAEL BEST & FRIEDRICH LLP

Grady J. Frenchick

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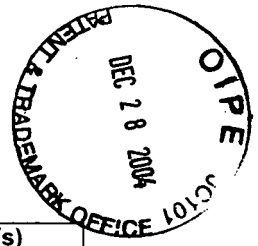

The Fischell et al. Applications and Patents Status

As of 12/02/2004

No	Filed	Title	Priority	Inventors	Published	Status	Examiner(s)
09/705,999	11/6/2000	Surgically Implanted Devices Having Reduced Scar Tissue Formation	First Application	Fischell	-	Abandoned	Kim Lewis
09/772,693	1/31/2001	Surgically Implanted Devices Having Reduced Scar Tissue Formation	CIP	Fischell	5/9/2002 3/18/2003	Issued Patent 6,534,693	Lalita Hamilton; Nicholas D. Lucchesi (S.P.E.)
10/072,177	2/11/02	Devices and methods for reducing scar tissue formation	CIP	Fischell	8/14/2003	Pending	Sharon Howard; Thurman Page (S.P.E.)
10/351,207	1/24/03	Surgically Implanted Devices Having Reduced Scar Tissue Formation	**Continuation of '693**	Fischell	1/8/2004	Pending	Kim Lewis
10/431,701	5/7/03	Compositions and Methods For Reducing Scar Tissue Formation	CIP	Fischell	1/29/2004	Pending	Thurman Page
10/449,162	5/30/03	Devices and Methods for Reducing Scar Tissue Formation	CIP	Fischell	4/15/2004	Pending	Not assigned yet
10/887,272	7/9/04	Not yet published, but likely to be "Devices and Methods for Reducing Scar Tissue Formation"	Claims priority of 722,693	Fischell	Un-published	Unpublished	

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and revised document: C:\DOCUME~1\LIR\LOCALS~1\TEMP\VCNEW\B0463362.DOC

CompareRite found 147 change(s) in the text

Deletions appear as Overstrike text
Additions appear as Bold text

United States Patent ~~6,534,693 Fischell, et al. March 18, 2003~~ Application **20040241211**
Kind Code **A9**
Fischell, Robert E. ; et al. **December 2, 2004**

~~Surgically implanted devices having reduced~~ **Devices and methods for reducing** scar tissue formation

Abstract

~~This invention is an anti-proliferative drug placed onto or within~~ **Disclosed is a cytostatic drug attached to** a sterile sheet ~~or mesh~~ that is designed to be placed between internal body tissues to prevent the formation of post-operative adhesions, which adhesions are really scar tissue formation. This ~~mesh or gauze~~ **sheet** onto or into which the drug is placed may be either a permanent implant or it may be biodegradable. By impregnating an existing product such as the Johnson & Johnson SURGICEL.TM. absorbable hemostat gauze-like sheet with an anti-proliferative drug such as ~~Rapamycin or Taxol~~ **sirolimus**, the biodegradable, drug impregnated mesh would act as a barrier to cell proliferation and hence be a deterrent to the formation of adhesions **or scar tissue**. Another embodiment of this invention is ~~an anti-proliferative~~ **a cytostatic** drug attached to a ~~bandage~~ **sheet** that is placed ~~onto a cut in the skin~~ **at the site of an anastamosis** to decrease scar tissue formation~~. Still another embodiment of the invention is an anti-proliferative drug that is attached to a surgical suture or coated onto a surgical staple both of which are used for connecting human tissues. The suture or staple then being more capable for decreasing cellular proliferation where the suture or staple material passes through the human tissue~~ **from within the vessel at the site of the anastomosis**.

Inventors **Fischell~~,~~, Robert E.**; *(Dayton, MD)* ; **Fischell~~,~~, David R.**; *(Fair Haven, NJ)* ;
: **Fischell~~, Tim A. (Richland, MI); Fischell, Scott J. S. (Glenelg, MD) Assignee: Afmedica, Inc. (Kalamazoo, MI) Appl. No.: 772693 Filed: January 31, 2001 Current U.S. Class: 602/43; 602/48 Intern'l Class: A61F 013/00 Field of Search: 606/151 424/78.01,422,427,428 514/912.44 623/66 128/898 602/41,43,46 604/890.1,891.1,304~~**

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514/291. 5496832 Mar., 1996 Armstrong 514/291. 5516781 May., 1996 Morris et al. 514/291. 5540931 Jul., 1996 Hewitt. 5552162 Sep., 1996 Lee. 5618553 Apr., 1997 Kelleher 424/428. 5624893 Apr., 1997 Yanni 514/2. 5693607 Dec., 1997 Segarini. 5708002 Jan., 1998 Luly et al. 514/291. 5756673 May., 1998 Sonnenshein et al. 530/350. 5795286 Aug., 1998 Fischell et al. 600/3. 5798334 Aug., 1998 Cutroneo. 5843156 Dec., 1998 Slepian et al. 128/898. 5912224 Jun., 1999 Donahoe et al. 514/2. 5912253 Jun., 1999 Cottens et al. 514/291. 5981568 Nov., 1999 Kunz et al. 514/411. 6015815 Jan., 2000 Mollison 514/291. 6060474 May., 2000 Williams. 6063396 May., 2000 Kelleher 424/428. 6117425 Sep., 2000 MacPhee et al. 424/94. 6124273 Sep., 2000 Drohan et al. 514/55. 6143037 Nov., 2000 Goldstein et al. 623/66. 6200985 Mar., 2001 Cottens et al. 514/291. 6221099 Apr., 2001 Anderson et al. 623/1. 6273908 Aug., 2001 Ndondo-Lay 623/1. Foreign Patent Documents WO01/87372 Nov., 2001 WO .

Other References

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Parent Case Text

REFERENCE TO A PREVIOUS PATENT APPLICATION This is a continuation-in-part application of the patent application Ser. No. 09/705,999 filed on Nov. 6, 2000., Tim A.; *(Richland, MI)*

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U.S. Current Class: 424/445
U.S. Class at Publication: 424/445
Intern'l Class: A61L 015/00

Claims

What is claimed is:

1. A **cytostatic anti-proliferative surgical wrap** sheet of material adapted for ~~implantation between~~ **being wrapped generally around** tissues of a human body **at the site of a surgical procedure**, the sheet of material ~~including an attached~~ **having a cytostatic** anti-proliferative drug~~, the~~ **attached, the action of the cytostatic** anti-proliferative drug being ~~designed to reduce~~ **a reduction in** the generation of scar tissue, the **cytostatic** anti-proliferative drug being selected from the group ~~consisting of Rapamycin, taclolimus (FK506), and one of the following analogs of sirolimus~~ **that includes sirolimus, anti-sense to c-myc (Resten-NG), tacrolimus (FK506), Everolimus and the any functional analog of sirolimus including**: SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin, 7-epi-thiomethyl-rapamycin, 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline.

2. The ~~apparatus~~ **cytostatic anti-proliferative surgical wrap** of claim 1 wherein the sheet of material is **drug eluting and** biodegradable.

3. The ~~apparatus~~ **cytostatic anti-proliferative surgical wrap** of claim 1 wherein the sheet of material is in the form of a mesh~~. 4. In combination, including an anti-proliferative drug attached to a bandage for placement over a cut on the skin of a human subject, the anti-proliferative drug~~ **that is drug eluting and biostable.**

4. The cytostatic anti-proliferative surgical wrap of claim 1 further including at least one additional medication attached to the wrap, the medication being selected from the group ~~consisting of taclolimus (FK506), Rapamycin and one of the following~~ **that includes an anti-biotic medication, an anti-inflammatory medication or an analgesic medication.**

5. In combination, a cytostatic anti-proliferative drug attached to a surgical suture, the suture being adapted to connect human tissue that is separated by a surgical procedure on a human subject, the cytostatic anti-proliferative drug being selected from the group that includes sirolimus, anti-sense to c-myc (Resten-NG), tacrolimus (FK506), Everolimus and the following functional analogs of sirolimus: SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-- rapamycin, 7-epi-thiomethyl-rapamycin, 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline.

~~5~~ **6**. In combination, ~~including an~~ **a cytostatic** anti-proliferative drug attached to a ~~surgical suture, the suture being adapted to connect human tissue that is separated by a surgical procedure on a human subject, the~~ **sheet for placement at an anastamosis of a vessel of the human body, the drug and sheet combination being adapted to prevent narrowing of the vessel at the site of the anastamosis of that vessel, the cytostatic** anti-proliferative drug being selected from the group ~~consisting of taclolimus (FK506), Rapamycin and one~~ **that includes sirolimus, anti-sense to c-myc (Resten-NG), tacrolimus (FK506), Everolimus or any other functional analog** of ~~the following analogs of~~ sirolimus **including**: SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin, 7-epi-thiomethyl-rapamycin, 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline.

~~6. In combination, including an anti-proliferative drug attached to a mesh having a generally cylindrical shape for introduction into a generally cylindrical cavity of the human body to decrease scar tissue formation in that generally cylindrical cavity after~~ **7. The combination of claim 6 wherein the sheet is in the form of a flat rectangle that is adapted to be placed around a vessel at the site of the anastamosis.**

8. The combination of claim 6 wherein the sheet is in the form of an annulus.

9. A means for improving the outcome of a surgical procedure on ~~that generally cylindrical cavity, the anti-proliferative drug~~ **a human subject, the means being the systemic release into the human subject on whom the surgical procedure has been performed of a cytostatic anti-proliferative agent in combination with at least one other drug selected from the group that includes antiseptic agents, anti-biotic agents and analgesic agents, the cytostatic anti-proliferative agent** being selected from the group ~~consisting of taclolimus (FK506), Rapamycin and one~~ **that includes sirolimus, anti-sense to c-myc (Resten-NG), tacrolimus (FK506), Everolimus and other analog** of ~~the following analogs of~~ sirolimus **including**: SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin, 7-epi-thiomethyl-rapamycin, 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline.

~~7. The combination of claim 6 wherein the generally cylindrical cavity is a human nostril. 8. A device to reduce scar tissue formation within the eye of a human subject after a retinal attachment procedure, including a buckle designed to be placed onto the eye, the buckle including an attached anti-proliferative, the anti-proliferative~~ **10. The means of claim 9 wherein additionally the cytostatic anti-proliferative agent is used in an ointment that is applied to the skin.**

11. The means of claim 9 wherein additionally the cytostatic anti-proliferative agent is attached to a mesh that is adapted to be placed within the human subject in whom the surgical procedure was performed.

12. The means of claim 9 wherein the cytostatic anti-proliferative agent is attached to a suture.

13. A method for decreasing the formation of scar tissue after a surgical procedure, the method comprising the following steps: a) attaching a cytostatic anti-proliferative drug onto a mesh that is adapted for placement generally around tissue of a human subject; the antiproliferative drug being selected from the group ~~consisting of taclolimus (FK506), Rapamycin and one~~ **that includes sirolimus, anti-sense to c-myc (Resten-NG), tacrolimus (FK506), Everolimus and any other analog** of ~~the following analogs of~~ sirolimus **including**: SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin- , 7-epi-thiomethyl-rapamycin, 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline. ~~9. An implantable device adapted for surgical implantation within a space within a human body at a location that is external to any vessel of that human body, at least part of the device including an attached~~ **b) placing the mesh with attached cytostatic** anti-proliferative drug~~, the action of the anti-proliferative drug being a reduction in the generation of scar tissue,~~

~~the anti-proliferative drug~~ **generally around tissue of the human subject during or after completing a surgical procedure.**

14. The method of claim 13 wherein the surgical procedure includes the forming of an anastamosis of a vessel of the human subject, the vessel being selected from the group ~~consisting of Rapamycin, taclolimus (FK506), and one of the following analogs of sirolimus:~~ **that includes an artery, a vein, a ureter, a urethra, an artificial graft, a jejunum, an ileum, a duodenum, a colon, a bile duct or a fallopian tube.**

15. The method of claim 13 further including the step of systemic application into the human subject of at least one cytostatic anti-proliferative drug at least one day prior to the surgical procedure.

16. The method of claim 13 further including the step of a continuing systemic application into the human subject of at least one cytostatic anti-proliferative drug for at least one day after the surgical procedure.

17. The method of claim 13 wherein the surgical procedure is the creation of an anastamosis to join a vein to the aorta of the human subject.

18. The method of claim 13 wherein the surgical procedure is the creation of an anastamosis to join an internal mammary artery to a coronary artery of the human subject.

19. A method for decreasing scar tissue formation on a cut in the skin of a human subject, the method comprising the following steps: a) placing an ointment onto the skin at the site of the cut, the ointment including a cytostatic anti-proliferative agent selected from the group that includes sirolimus, anti-sense to c-myc (Resten-NG), tacrolimus (FK506), Everolimus or any other functional analog of sirolimus including: SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin, 7-epi-thiomethyl-~~rapamycin~~, 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline~~. 10. The device of claim 9 wherein the device is in the form of a prosthetic breast implant. 11. The device of claim 9 wherein the device is in the form of an arterio-venus fistula shunt. 12. A method for improving the outcome of a surgical procedure, the method being the release into a human subject on whom the surgical procedure has been performed of an anti-proliferative agent in combination with at least one other drug~~**; and b) placing a bandage over the ointment, the bandage being attached to the skin in the vicinity of the cut.**

20. The method of claim 19 including the step of placing into the ointment at least one additional therapeutic agent that is selected from the group that includes an antiseptic drug, an anti-biotic drug and an analgesic drug.

21. The method of claim 19 further including the step of the systemic administration of at least one cytostatic anti-proliferative agent selected from the group ~~consisting of antiseptic agents, anti-biotic agents and analgesic agents, and the anti-proliferative agent being selected from the group consisting of Rapamycin, taclolimus (FK506), and one of the following analogs~~

~~of sirolimus~~ **that includes sirolimus, anti-sense to c-myc (Resten-NG), tacrolimus (FK506), Everolimus and any other functional analog of sirolimus including**: SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin, 7-epi-thiomethyl-rapamycin, ~~7-demethoxy-rapamy-cin, 32-demethoxy, 2-desmethyl and proline. 13. The method of claim 12 wherein the anti-proliferative agent is used in an ointment that is applied to the skin. 14. The method of claim 12 wherein the anti-proliferative agent is attached to a mesh that is adapted to be placed within the human subject in whom the surgical procedure was performed. 15. The method of claim 12 wherein the anti-proliferative agent is attached to a breast implant. 16. The method of claim 12 wherein the anti-proliferative agent is attached to a suture. 17. The method of claim 12 wherein the anti-proliferative agent is released systemically. 18. A method for decreasing the formation of scar tissue after a surgical procedure, the method comprising the following steps: a) attaching an anti-proliferative drug onto a sheet of material designed to be placed onto or into a human subject; the anti-proliferative drug being selected from the group consisting of Rapamycin, taclolimus (FK506), and one of the following analogs of sirolimus: SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin, 7-epi-thiomethyl-rapamycin, 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline; and b) placing the mesh with the attached anti-proliferative drug onto or into a human subject during or after completing a surgical procedure. 19. The method of claim 18 further including the step of systemic application of at least one anti-proliferative drug at least one day prior to the surgical procedure. 20. The method of claim 18 further including the step of a continuing systemic application of at least one anti-proliferative drug for at least one day after the surgical procedure. 21. In combination, an anti-proliferative drug attached to a breast implant, the breast implant being designed to provide breast enlargement for a human female subject, the anti-proliferative drug being selected from the group that includes taclolimus (FK506), Rapamycin and the following analogs of sirolimus: SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin, 7-epi-thiomethyl-rapamycin,~~ 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline.

22. A sheet for placement at or near the site of a surgical procedure to reduce the formation of scar tissue and adhesions, the sheet including a cytostatic drug that is released from the mesh or sheet over a period that is longer than a day, the cytostatic drug being capable of preventing the initiation of DNA replication of cells in the vicinity of the mesh by acting as a cell cycle mitosis inhibitor that acts on the cells in the vicinity of the mesh at or before the S-phase of cellular mitosis.

Description

FIELD OF USE

[0001] This invention is in the field of ~~materials~~ **devices and methods** used to prevent the formation of scar tissue ~~subsequent to~~ **that often occurs as a result of** a surgical procedure ~~or accidental skin cut of a human subject~~.

BACKGROUND OF THE INVENTION

~~Post-operative adhesions are a major problem following abdominal and other surgical procedures. These adhesions are~~**[0002] Post-operative scar tissue formation, adhesions and blood vessel narrowing are major problems following abdominal, neurological, vascular or other types of surgery. For example, narrowing of a blood vessel at the site of an anastamosis is often** caused by the unwanted proliferation of scar tissue ~~between internal tissues and structures of the human body generally after surgery. Several~~ **at that location.**

[0003] U.S. patent application Ser. No. 09/772,693 by R. E. Fischell, et al, filed on Jan. 1, 2001 describes various means and methods to reduce scar tissue formation resulting from a surgical procedure. However, this patent application does not describe a cytostatic anti-proliferative surgical wrap that is placed around some human tissue where there is a risk of formation of scar tissue. Although several companies have developed **products (such as** sheets of biodegradable mesh**, gels, foams and barrier membranes of various materials)** that can be placed between these structures to reduce the tissue growth~~. None~~**, none** are entirely effective ~~as some scar tissue typically grows through the mesh.~~**.**

[0004] U.S. Pat. No. 5,795,286 describes the use of a beta emitting radioisotope ~~to reduce the proliferation of tissue through a biocompatible material placed into the human body~~ **placed onto a sheet of material to reduce scar tissue formation by means of irradiation of the local tissue**. Although radioisotopes may be effective at preventing ~~the cell~~ **cellular** proliferation associated with adhesions, the limited shelf life and safety issues associated with radioisotopes ~~makes~~ **make** them less than ideal for this purpose.

[0005] Recent publications ~~(Transcutaneous~~**(Transcatheter** Cardiovascular Therapeutics ~~2000~~ **2001** Abstracts) report a greatly reduced ~~cell~~ **cellular** proliferation **and reduced restenesis** within angioplasty injured arteries when vascular stents used for recannalization are coated with ~~an~~ **a cytostatic** anti-proliferative drug such as Rapamycin ~~(Sirolmus)~~**(sirolmus), Actinomycin-D** or Taxol. However, these drugs have never been used for reducing cellular proliferation **at the site** of ~~tissues separated by~~ a surgical procedure.

~~SUMMARY OF THE INVENTION A first~~**[0006] In U.S. Pat. No. 6,063,396, P. J. Kelleher describes the use of highly toxic, antimitotic drugs such as ricin, anthracycline, daunomycin, mitomycin C and dexorubin for reducing scar tissue formation and for wound healing. However, he makes no mention of any cytostatic anti-proliferative drug such as sirolimus or similar acting compounds.**

[0007] In U.S. Pat. No. 5,981,568 Kunz et al describe the use of certain cytostatic agents that are used to inhibit or reduce restenosis of an artery that is treated from inside that artery. However, Kunz et al does not address the problem of restenosis at an anastamosis which is the surgical connection of two blood vessels. Kunz et al also fails to consider the drug sirolimus or its functional analogs as the drug to be applied for reducing cellular proliferation that can result in scar tissue formation or adhesions.

SUMMARY OF THE INVENTIONS

[0008] **One** embodiment of this invention is a device consisting of ~~a~~ **cytostatic anti-proliferative** drug impregnated into, coated onto or placed onto a material sheet or mesh designed to be placed ~~between internal body tissues that have been surgically separated to prevent the formation of~~ **generally around human tissue that has been surgically joined or surgically treated; the goal being the prevention of formation of excess** post-operative ~~adhesions, which adhesions are really~~ scar tissue ~~formation~~. A drug that is impregnated into a **suture or** gauze-like material or **sheet or** coated onto the material or joined to the material by adhesion and/or capillary action is defined herein as a drug ~~"attached"~~**"attracted"** to a **suture or** mesh **or sheet**. This **suture,** mesh or gauze onto which the drug is attached may be either a permanent implant or it may be biodegradable. The drug can be attached to an existing product such as the Johnson & Johnson SURGICEL.TM. absorbable hemostat gauze-like sheet **or a Vicryl mesh product**. With ~~an~~ **a cytostatic** anti-proliferative drug such as ~~Rapamycin or Taxol~~ **sirolimus or its functional analogs** which have a known effect on proliferating cells, the **drug released from the** biodegradable mesh would decrease cellular proliferation and hence be a deterrent to the formation of ~~adhesions.~~ **excess scar tissue at the surgical site.**

[0009] It is also envisioned that ~~an anti-proliferative drug attached to a bandage could be placed onto a cut in the skin for reducing scar tissue formation. This cut could be accidental or a result of a surgical incision. It is also envisioned that an~~ **a cytostatic** anti-proliferative drug could be attached to surgical suture material ~~that is~~. **This suture/drug combination could be** used (for example) to join together two blood ~~generally cylindrical cavitys,~~ **vessels;** i.e., an anastomosis, with the attached drug causing a reduction in cellular proliferation in the vicinity where the sutures penetrate through the ~~human tissue~~ **wall of the vessel. A suture material with a cytostatic, antiproliferative drug attached that decreases scar tissue formation would also be useful for sutures in the skin, particularly for plastic surgery. A very important application would be for sutures that are required for eye surgery where reduced scar tissue formation is very much needed**. It should be understood that the suture material could be either soluble or insoluble and could be used for any application for which sutures are used.

[0010] Still another embodiment of the present invention is ~~an~~ **a cytostatic** anti-proliferative drug coated onto a surgical staple thus reducing scar tissue around that staple.

~~Still another embodiment of this invention is to attach an~~**[0011] In addition to applying the cytostatic** anti-proliferative drug ~~to a device such as a buckle that is used for the treatment of a detached retina. Since scar tissue formation is one of the main complications of a retinal attachment procedure, by attaching an~~ **at the surgical site by means of a device to which the cytostatic** anti-proliferative drug ~~to the buckle that is placed around the eye, there can be some reduction in scar tissue formation. It~~ **is attached, it** is also envisioned to ~~attach an~~ **apply the least one day from the material onto which they are attachable. In describing this invention, the use of the terms "mesh" or "sheet" or "gel" shall mean the same thing (i.e., a material to which or into which a cytostatic drug is attached) and these words will be used interchangeably. The present invention ideally utilizes those cytostatic drugs, such as sirolimus or Everolimus, that interfere with the initiation of mitosis by means of interaction with TOR protein complex formation and cyclin signaling. These drugs prevent the initiation of DNA replication by acting on cells in close proximity to the mesh from which the drug slowly elutes as very early cell cycle mitosis inhibitors that act at or before the S-**

phase of cellular mitosis.

[0012] Thus it is an object of this invention to have a sheet of material that can be placed into or wrapped generally around some human tissue at the site of a surgical procedure, the material having a cytostatic anti-proliferative drug attached ~~to the outside of a cylindrical tube that is placed within a generally cylindrical cavity of the human body to decrease~~ **for reducing** scar tissue formation ~~after a surgical procedure on that generally cylindrical cavity. Such a generally cylindrical cavity might be a nostril after an operation for a deviated septum, a fallopian tube, a billiary duct, a urethra, (for example after prostate surgery) a ureter, a bronchial tube, etc. For such an application, the tube with the attached anti-proliferative drug could be biodegradable, remain implanted or it could be removed after a few days or weeks. Another device that would benefit from a coating of an anti-proliferative agent such as Rapamycin is a prosthetic implant that is placed into a woman's breast after reconstructive or augmentative surgery. Breast implants typically form significant scar tissue around their surface after implantation. Coating the surface of the breast implant with a slowly releasing anti-proliferative agent can significantly reduce this scar tissue formation. Still another application of these concepts is for aterio-venous fistulas that are used for kidney dialysis patients. These devices (which are also called a-v shunts) are used to connect an artery in an arm to a large vein in the same arm. The plastic a-v shunt is then penetrated by comparatively large needles through which the patient's blood is cleansed typically every other day. A frequent cause of failure for these shunts is caused by proliferative cell growth at the anastamosis where the shunt is joined to a vein. By having sutures coated with an anti-proliferative agent and by coating the interior and/or exterior of the a-v shunt with an anti-proliferative agent it is expected that the time for maintaining adequate blood flow through the vein will be extended. In addition to applying the anti-proliferative drug by means of a device to which the anti-proliferative drug is attached, it is also envisioned to apply the anti-proliferative drug systemically by any one or more of the well known means for introducing a drug into a human subject. For example, an anti-proliferative drug could be applied by oral ingestion, by a transdermal patch, by a cream or ointment applied to the skin, by inhalation or by a suppository. Any of these methods being a systemic application of an anti-proliferative drug. It should be understood that such a drug should be applied systemically starting at least one day prior to a surgical procedure but could be started as long as 5 days prior to a surgical procedure. Furthermore, the drug should be applied for a period of at least one day after the procedure and for some cases as long as 60 days. It should be understood that an anti-proliferative drug could be given systemically without using any of the devices described herein. Preferably, the anti-proliferative drug would be given systemically in addition to the application of an anti-proliferative drug attached to any one or more of the devices described herein. It should also be understood that an optimum result might be obtained with using one anti-proliferative drug attached to a device with a second and/or third drug being used for systemic administration. A typical dose for a patient, for example with Rapamycin, would be 1.5 mg/kg per day. The dose would of course depend on the anti-proliferative drug that was used. Thus it is an object of this invention to have a sheet of material that can be placed between internal body tissues, the material having an anti-proliferative drug attached to reduce scar tissue formation between adjacent layers of the human tissue. Another object of this invention is to have a biodegradable sheet of material or mesh suitable for placement between body tissues including an attached drug that prevents the cellular proliferation associated with post-surgical adhesions. Still another object of the invention is to have a bandage to which an anti-proliferative**

~~drug is attached that is placed onto a cut in the skin to reduce scar tissue formation. Still another object of the invention is to have a suture material or surgical staple to which an anti-proliferative drug is attached. Still another object of the invention is to have an anti-proliferative drug attached to the exterior of a cylindrical tube that is placed into a generally cylindrical cavity of the human body after a surgical procedure on that generally cylindrical cavity. Still another object of the invention is to have a device implanted in a human subject, the device having an anti-proliferative agent attached; the device being a breast implant, an a-v shunt or an equivalent device for implantation into the human subject. Still another object of this invention is to have the anti-proliferative drug be Rapamycin or an equivalent drug. Still another object of this invention is to have the anti-proliferative drug be Taxol or an equivalent drug. Still another object of the invention is to employ a device placed into or onto the body of a human subject, which device has an attached anti-proliferative drug, plus using the same or a different anti-proliferative drug as a medication to be applied systemically to the human subject from some time prior to a surgical procedure to some time after that procedure. These and other objects and advantages of this invention will become obvious to a person of ordinary skill in this art upon reading of the detailed description of this invention including the associated drawings. BRIEF DESCRIPTION OF THE DRAWINGS FIG. 1 is a plan view of a sheet or mesh onto which an anti-proliferative drug has been attached. FIG. 2 is an enlargement of the cross section of a single strand of the mesh where the drug is embedded within the strand. FIG. 3 is an enlargement of the cross section of a single strand of the mesh where the drug is coated onto the strand. FIG. 4 is an enlargement of two strands of the mesh that have been dipped into a solution of an anti-proliferative drug thereby attaching the drug to the strands by adhesion and capillary action. FIG. 5 shows a cross section of the mesh to which an anti-proliferative drug has been attached, the mesh being placed between two layers of tissue of the human body. FIG. 6 is a cross section of the skin onto which is taped a bandage to which an anti-proliferative drug has been attached. FIG. 7 is a cross section of a human breast into which a breast implant has been placed. FIG. 8 illustrates a buckle used for the treatment of detached retina. DETAILED DESCRIPTION OF THE DRAWINGS FIG. 1 shows an absorbable hemostat mesh sheet 10 with mesh strands 12 and open spaces 11. The sheet 10 is designed to be placed post-operatively between internal body tissues that have been separated by a surgical procedure. The mesh strands 12 can be made from oxidized regenerated cellulose or other biodegradable materials with the~~ **at the site of the surgical procedure.**

[0013] Another object of this invention to have a sheet of material that can be wrapped around a blood vessel, a ureter, a bile duct, a fallopian tube, or any other vessel of the human body at the site of a surgically created anastamosis, the material having a cytostatic anti-proliferative drug attached to reduce scar tissue formation that can result in a narrowing of the vessel or duct at the site of anastamosis.

[0014] Still another object of this invention is to have a biodegradable sheet of material or mesh suitable for placement between body tissues including an attached drug that elutes slowly from the sheet of material to prevent cellular proliferation associated with post-surgical adhesions and/or scar tissue formation.

[0015] Still another object of the invention is to have a suture material or surgical staple to which a cytostatic anti-proliferative drug is attached.

[0016] Still another object of this invention is to have the cytostatic anti-proliferative drug be sirolimus or a functionally equivalent cytostatic and anti-inflammatory drug.

[0017] Still another object of the invention is to employ a device placed into the body of a human subject, which device has an attached cytostatic anti-proliferative drug, plus using the same or a different cytostatic anti-proliferative drug as a medication to be applied systemically to the human subject from some time prior to a surgical procedure and/or for some time after that procedure in order to reduce excessive post-surgical scar tissue formation.

[0018] These and other objects and advantages of this invention will become obvious to a person of ordinary skill in this art upon reading of the detailed description of this invention including the associated drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] FIG. 1 illustrates a sheet of material to which a cytostatic anti-proliferative drug has been attached; the sheet is formed so that it can be wrapped around or placed on or between human tissue at the site of a surgical procedure.

[0020] FIG. 2 is an enlargement of the cross section of a single strand of the mesh where the drug is embedded within the strand.

[0021] FIG. 3 is an enlargement of the cross section of a single strand of the mesh where the drug is coated onto the strand.

[0022] FIG. 4 is an enlargement of two strands of the mesh that have been dipped into a solution of a cytostatic anti-proliferative drug thereby attaching the drug to the strands by adhesion and capillary action.

[0023] FIG. 5 is a lateral cross section of cytostatic anti-proliferative surgical wrap placed around an end-to-end anastamosis of a vessel or duct.

[0024] FIG. 6 is a layout view of the surgical wrap of FIG. 5.

[0025] FIG. 7 is a plan view of an annular anti-proliferative sheet for application to anastamoses.

[0026] FIG. 8 is a plan view of a annular anti-proliferative sheet for application to anastamoses, the interior of the annulus having slits to facilitate placement onto a connecting blood vessel.

[0027] FIG. 9 is a cross section of cytostatic anti-proliferative surgical wrap placed at an aorta-vein graft anastamosis.

[0028] FIG. 10 is a cross section of cytostatic anti-proliferative surgical wrap placed at the anastamosis of the internal mammary artery into the side of a coronary artery.

DETAILED DESCRIPTION OF THE INVENTION

[0029] FIG. 1 shows an absorbable mesh sheet 10 with mesh strands 12 and open spaces 11. The sheet 10 is designed to be placed post-operatively into or around human tissue at the site of a surgical procedure. When placed at the site of a surgical procedure, the sheet 10 is designed to slowly elute a cytostatic drug so as to decrease the formation of scar tissue and to reduce the extent of adhesions. When placed generally around human tissue, the mesh 10 forms a cytostatic anti-proliferative surgical wrap. The mesh strands 12 can be made from oxidized regenerated cellulose or other biodegradable materials with the cytostatic anti-proliferative drug either embedded within the strands, coated onto the outer surfaces of the strands or held onto the strands by adhesion or capillary action. Any of these possibilities will be described herein as the drug being attached to the mesh or attached to the strand of the mesh.

[0030] FIG. 2 is an enlargement of a cross section of a single strand 12 of the mesh 10 in which the **cytostatic** anti-proliferative drug 14 is embedded within the strand 12.

[0031] FIG. 3 is an enlargement of the cross section of a single strand 12 of the mesh where the **cytostatic** anti-proliferative drug ~~17 is coated~~ **is placed into a coating 17 formed** onto the exterior surface of the strand~~.~~ **12. The strand 12 could be formed from either a biostable or biodegradable polymer material. The material of the coating 17 is selected so that the drug that is placed into the coating 17 will slowly elute into the human tissue at the site of a surgical procedure. To further adjust the rate of release of the drug into adjacent tissue, the coating 17 could be covered with an additional coating (not shown).**

[0032] FIG. 4 is an enlargement of two adjacent strands 12 of the mesh 10 onto which ~~an~~ **a cytostatic** anti-proliferative drug 18 is attached by means of adhesion and capillary action.

~~FIG. 5 shows the anti-proliferative drug attached to the mesh 10 placed between two adjacent tissues 20 and 21 of a human body. The mesh 10 would be inserted during a surgical procedure typically just before closing of the surgical incision. When the biodegradable mesh 10 dissolves or is absorbed into the tissues 20 and 21, the anti-proliferative drug attached to the mesh 10 will become dispersed into the tissues 20 and 21. On the other hand, if the biocompatible sheet of material is not biodegradable, the anti-proliferative drug will remain at the site where it is placed for a longer period of time than if the material sheet is biodegradable. Similarly, the drug itself may be produced in a soluble or insoluble form. An insoluble form would remain at the treatment site longer than a soluble form.~~**[0033]** The anti-proliferative drugs that ~~may be used~~ **are less suitable for this purpose** include **cytotoxic** cancer drugs such as Taxol ~~and other known anti-proliferative drugs such as Rapamycin. Other drugs that could be used are~~**, Actinomycin-D,** Alkeran, Cytoxan, Leukeran, Cis-platinum, BiCNU, Adriamycin, Doxorubicin, Cerubidine, Idamycin, Mithracin, Mutamycin, Fluorouracil, Methotrexate, Thoguanine, ~~Toxotere~~ **Texotere**, Etoposide, Vincristine, Irinotecan, Hycamptin, Matulane, Vumon, Hexalin, Hydroxyurea, Gemzar, Oncovin and Etophophos~~, tacrolimus (FK506), and the following analogs of sirolimus: SDZ-RAD, CCI-779~~**. The optimum drugs for this purpose do include cytostatic**

drugs such as sirolimus, anti-sense to c-myc (Resten-NG), tacrolimus (FX506), Everolimus and any other analog of sirolimus including: SDZ-RAD, CCI-770, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin- , 7-epi-thiomethyl-rapamycin, 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline.

[0034] Although a mesh has been discussed herein, more generally, ~~an~~ **a cytostatic** anti-proliferative drug can be made to be part of any sheet of material that is or is not biodegradable, as long as the sheet of material is biocompatible. In any case ~~the effect of the anti-proliferative drug that is attached to at least part of the sheet of material will decrease cellular proliferation and therefore decrease the formation of scar tissue and adhesions. It should also be understood that the mesh 10 could be rolled into a cylinder and placed into a generally cylindrical cavity of the human body that has undergone a surgical procedure. The mesh 10, in a cylindrical form, could also be placed around an elastomer tube prior to placement in the human generally cylindrical cavity. FIG. 6 is a cross section of a cut 23 in the skin 22 that is situated above the subcutaneous tissue 24. A bandage 25 to which an anti-proliferative drug has been attached is shown attached to the skin 22 by means of an adhesive tape 26. The purpose of the anti-proliferative drug is to reduce scar tissue formation in order to have an improved appearance of the skin. The bandage may also include an antiseptic agent to decrease the possibility of infection. It should also be understood that an ointment that includes an anti-proliferative agent could be used separately from the bandage 25 of FIG. 6. The anti-proliferative agent would be selected from the group that includes Alkeran, Cytoxan, Leukeran, Cis-platinum, BiCNU, Adriamycin, Doxorubicin, Cerubidine, Idamycin, Mithracin, Mutamycin, Fluorouracil, Methotrexate, Thoguanine, Toxotere, Etoposide, Vincristine, Irinotecan, Hycamptin, Matulane, Vumon, Hexalin, Hydroxyurea, Gemzar, Oncovin and Etophophos, taclolimus (FK506), and the following analogs of sirolimus: SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin, 7-epi-thiomethyl-rapamycin, 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline. Another alternative embodiment of the invention is a suture material to which an~~, **this material should gradually release the cytostatic anti-proliferative drug into the surrounding surgically injured tissue over a period from as short as a day to as long as a few months. The rate of release being controlled by the type of material into which the drug is placed. It is also envisioned that a polymer coating could be placed over the drug to slow the eluting of the drug into the surrounding tissue. Such polymer materials are well known in the field of slow release of medications, and one example is described in some detail in U.S. Pat. No. 6,143,037 by S. Goldstein et al. The effect of the cytostatic anti-proliferative drug that is attached to at least part of the sheet of material will decrease cellular proliferation and therefore decrease the formation of scar tissue and/or adhesions. Most importantly, such a mesh 10 wrapped around a vascular anastamosis would reduce the narrowing of that vessel which often occurs at the site of the anastamosis.**

[0035] FIG. 5 is a cross section of a cytostatic anti-proliferative surgical wrap 21 shown wrapped around an anastamosis of a vessel or duct, the sutures 22 being used to join the cut ends of the vessel or duct. The vessel or duct can include, but is not limited to, a vein, an artery, the joining of an artificial graft to a vein or artery, a ureter, a urethra, a bile duct, an ileum, a jejunum, a duodenum, a colon or a fallopian tube. Such a wrap could be used anywhere at a site where a surgical procedure has been done. For example, the surgical site

might be at the site of operations on the backbone, nerves coming out of a verterbrae, the colon or ileum, etc. A cytostatic anti-proliferative surgical wrap is defined herein as a game-like mesh that is wrapped generally around some human tissue at the site of a surgical procedure. The wrapping could be somewhat more or less than a full 360-degree wrap around the tissue. To accommodate tissues having different diameters, the wrap material could be sterilized in comparatively long lengths and the surgeon could it to the correct length at the time of surgery. This wrap can be sutured in place with either a conventional suture or with sutures to which a cytostatic anti-proliferative drug has been attached. FIG. 6 shows such a wrap 21 having ends 23 and 24, which ends are typically sutured onto the vessel that has an anastamosis.

[0036] FIG. 7 shows an annular sheet 25 having a cut 26; the sheet 25 would have an anti-proliferative drug attached to it. The use of this sheet 25 will be explained below with the assistance of FIGS. 9 and 10. FIG. 8 shows a slit annular sheet 27 that has a cut 28 end slits 29. This type of slit annular sheet is particularly well suited for being sutured onto the aorta at the site of an anastamosis with the sections between the slits 29 being placed and sutured onto the blood that is joined to the aorta.

[0037] FIG. 9 illustrates a typical anastamosis that occurs during coronary bypass surgery; namely, a blood vessel (typically a vein from the patient's leg) surgically joined to the aorta by sutures 31 and 32. FIG. 9 shows the surgical wrap 21 attached to the blood vessel by means of at least one suture 35. Also shown in FIG. 9 is an annular sheet 25 attached to the aorta by means of sutures 33 and 34. The wrap 21 and sheet 25 would each have attached an anti-proliferative drug as described herein to prevent the formation of scar tissue, within the blood vessel and within the aorta. Such an anastamosis is a frequent site where the formation of scar tissue diminishes the flow of blood through the blood vessel. By the slow release of an anti-proliferative drug attached to the wrap 21 and the sheet 25, there will be a decreased incidence of sterosis at the site of the anastamosis. It should be understood, that either the wrap 21 or the sheet 25, separately or together, could be used at this type of anastamosis.

[0038] FIG. 10 illustrates a typical coronary artery bypass graft of an artery or a vein to a coronary artery. FIG. 10 specifically shows an internal mammary artery surgically joined to a coronary artery such as the left anterior descending, left circumflex or right main coronary artery. To avoid the formation of scar tissue inside the anastamosis, a slit annular sheet 27 (as shown in FIG. 8) has been sutured to the coronary artery and the internal mammary artery by means of the sutures 36, 37, 38 and 39. It should be understood that the wrap 21 and/or the sheet 25 could also be applied at this site. Furthermore, the surgeon could cut away some of the sheet located between the slits 29 of the sheet 27 before attaching it by sutures to the site of the anastamosis. Although FIG. 9 shows an anastamosis between the internal mammary artery and a coronary artery, any suitable vein could also be used in place of the internal mammary artery.

[0039] Another alternative embodiment of the invention is a suture material to which a cytostatic anti-proliferative drug is attached. A drawing of a highly enlarged cross section of such a suture would be shown by FIGS. 2 or 3. That is, FIG. 2 could be considered to be a cross

section of a suture 12 into which is embedded ~~an~~ **a cytostatic** anti-proliferative drug 14. FIG. 3 could be considered a highly enlarged cross section of a suture 12 that is coated with ~~an~~ **a cytostatic** anti-proliferative drug 17. **FIG. 5 shows cytostatic anti-proliferative coated sutures 22 used to join a vascular anastamosis.** The object of attaching ~~an~~ **a cytostatic** anti-proliferative drug to a suture would be to reduce scar tissue formation where the suture penetrates through human tissue. This would be particularly true for the use a suture to join together two ~~generally cylindrical cavitys~~ **vessels**, i.e., an anastamosis. This could be used for both soluble and insoluble suture materials. ~~Furthermore, an~~ **By using a suture to which a cytostatic anti-proliferative drug is attached, a surgeon would have a method for reducing scar tissue formation on the surface of the skin or anywhere else where sutures are used. A particularly valuable place for such sutures would be for eye or plastic surgery where scar tissue formation can compromise the result of a surgical procedure. Furthermore, a cytostatic** anti-proliferative drug could be attached to any surgical staple that is used to join together human tissue after a surgical procedure. It should be understood that sutures or staples with ~~an~~ **a cytostatic** anti-proliferative agent attached could be used for joining any tissue of a human subject where it is desired to reduce cellular proliferation, i.e., the formation of adhesions or scar tissue. ~~FIG. 7 illustrates the implant into the breast of a human subject of a breast implant 31. Attached to the breast implant 31 would be an anti-proliferative agent~~ **It should also be understood that any of the sutures 22, 31, 32, 33, 34, 35, 36, 37, 38 or 39 as shown in FIGS. 5, 9 and 10 could be conventional sutures or could have a cytostatic drug as described herein attached to that suture.**

[0040] When cytostatic anti-proliferative sutures are used on the skin's surface, it should be understood that an ointment that includes a cytostatic anti-proliferative agent could be applied to the skin at the site of a surgical incision. The cytostatic anti-proliferative agent would be selected from the group that includes ~~Rapamycin, Taxol, Alkeran, Cytoxan, Leukeran, Cis-platinum, BiCNU, Adriamycin, Doxorubicin, Cerubidine, Idamycin, Mithracin, Mutamycin, Fluorouracil, Methotrexate, Thoguanine, Toxotere, Etoposide, Vincristine, Irinotecan, Hycamptin, Matulane, Vumon, Hexalin, Hydroxyurea, Gemzar, Oncovin and Etophophos, taclolimus (FK506), and the following analogs of sirolimus:~~ **sirolimus, anti-sense to c-myc (Resten-NG), tacrolimus (FK506), Everolimus and any other analog of sirolimus including** SDZ-RAD, CCI-779, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin, 7-epi-thiomethyl-rapamycin, 7-demethoxy-rapamycin, 32-demethoxy, 2-desmethyl and proline.

~~When a breast implant has an attached anti-proliferative agent, the scar tissue that typically forms around such an implant will be significantly reduced.~~**[0041]** If an arterio-venus fistula shunt is placed into the arm of a ~~dialysis~~ **dialyses** patient, then the same type of **cytostatic** anti-proliferative agent(s) as described above could be attached to that ~~implanted~~ **shunt** device to increase the time during which the associated vein in the arm would remain patent. ~~Another application of the present invention is for prevention of scar tissue formation subsequent to a procedure for attaching a detached retina. This procedure uses what is called a "buckle" placed around the eye to cause re-attachment of the retina. The extent of scar tissue formation after this procedure is performed can be decreased by attaching an anti-proliferative drug to the buckle. FIG. 8 illustrates a buckle 40 having an attached anti-proliferative drug coating 42 that is wrapped around an eye for the treatment of a detached retina. FIG. 8 also shows an enlarged~~

~~cross-section of the buckle 40 with the coating 42 attached on the buckle's outer surface. It should be understood that the~~ **Ideally, the cytostatic** anti-proliferative drug could ~~also be contained within the material of the buckle 40.~~ **be placed throughout the inner surface of the shunt or it could be placed near the ends where the shunt attaches to the vein or to the artery.**

[0042] For any of the applications described herein, the systemic application of one or more of the **cytostatic** anti-proliferative agents that have been described could be used conjunctively to further minimize the creation of scar tissue.

[0043] Although only the use of certain **cytostatic** anti-proliferative agents has been discussed herein, it should be understood that other medications could be added to the **cytostatic** anti-proliferative drugs to provide an improved outcome for the patients. Specifically, for applications on the skin, an antiseptic, and/or anti-biotic, and/or analgesic**, and/or anti-inflammatory** agent could be added to ~~an~~ **a cytostatic** anti-proliferative ointment to prevent infection and/or to decrease pain. These other agents could also be applied for any other use of the **cytostatic** anti-proliferative drugs that are described herein~~. It~~ **it** is further understood that any human subject in whom ~~an~~ **a cytostatic** anti-proliferative agent is used plus at least one of the other drugs listed above could also benefit from the systemic administration of one or more **cytostatic** anti-proliferative agent that has been listed herein.

[0044] Various other modifications, adaptations, and alternative designs are of course possible in light of the above teachings. Therefore, it should be understood at this time that within the scope of the appended claims, the invention can be practiced otherwise than as specifically described herein.